

The ALSFRS_r predicts survival time in an ALS clinic population

P. Kaufmann, MD, MSc; G. Levy, MD; J.L.P. Thompson, PhD; M.L. DelBene, NP-P, RN, MS; V. Battista, BA; P.H. Gordon, MD; L.P. Rowland, MD; B. Levin, PhD; and H. Mitsumoto, MD

Abstract—Objective: To determine whether the Amyotrophic Lateral Sclerosis Functional Rating Scale–revised (ALSFRS_r), a predictor of survival time in ALS clinical trials, predicts survival time in an ALS clinic population. **Methods:** The authors prospectively evaluated 267 consecutive patients with ALS at first visit to an ALS clinic using the ALSFRS_r and pulmonary function testing. The association of ALSFRS_r score at baseline with death or tracheostomy in ALS was examined using Cox proportional hazards models, adjusting for age at baseline, sex, and symptom duration. **Results:** Of 267 patients with ALS, 103 (39%) reached the endpoint, defined as either death (79 patients) or tracheostomy (24 patients), during a mean follow-up of 1.0 ± 0.7 years. Among the 103 patients who reached the endpoint during follow-up, 77 (75%) had a baseline ALSFRS_r score of less than 38 (the median baseline score of all patients), compared to 53 of 164 (32%) who remained alive without tracheostomy. Patients with a total ALSFRS_r score below the median had a 4.4-fold increased risk of death or tracheostomy compared to those who scored above the median (HR: 4.38, 95% CI: 2.79 to 6.86, $p < 0.001$). Both the total ALSFRS_r score at baseline (HR: 0.94, 95% CI: 0.91 to 0.98, $p < 0.001$) and forced vital capacity at baseline (HR: 0.99, 95% CI: 0.98 to 1.00, $p = 0.02$) were associated with death or tracheostomy when included in the same Cox model. **Conclusions:** In an ALS clinic population, the total Amyotrophic Lateral Sclerosis Functional Rating Scale–revised score at baseline is a strong predictor of death or tracheostomy independently of forced vital capacity and after adjustment for age at baseline, sex, and symptom duration.

NEUROLOGY 2005;64:38–43

Clinical trials in ALS have used the following primary outcomes: mortality,^{1–4} pulmonary function,⁵ muscle strength,^{6–8} and neurologic impairment and disability.^{9,10} The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) or its revised version (ALSFRS_r), a disease-specific functional rating scale, was a secondary outcome measure in several trials.^{2,3,5,7,8,11} Favorable properties of the scale include the following: 1) It is patient-centered, measuring function from the patient's perspective. 2) It is cost-efficient and, unlike muscle strength testing, does not require special equipment. 3) Administration by telephone shows good correlation with in-clinic administration and can be used when patients can no longer travel to the clinic.¹² 4) Internal consistency and test-retest reliability are excellent.^{13,14} 5) Construct validity is evident because it correlates well with a non-disease specific, validated functional rating scale, the Sickness Impact Profile (SIP),^{15–16} with the Schwab and England Scale, a widely used instrument to score activities of daily living,¹⁵ and with measures of muscle strength.¹³ 6) Most importantly, it has been validated as predictor of survival time based on data from ALS trials.^{2,14,16,17}

The generalizability of the finding that the ALSFRS_r is a predictor of survival time is unclear for several

reasons. First, the follow-up time in some of the clinical trials was limited to the relatively short period of 6 to 9 months.^{2,7,9,11,14,16} Second, patients who did not meet all El Escorial criteria for probable or definite ALS were excluded.^{2,3,5,7,8,14,16,17} Third, studies using quantitative muscle strength testing as primary outcome measure excluded both patients with bulbar and respiratory ALS and patients who were unable to perform quantitative strength testing due to advanced muscle weakness.^{7,8,11,16,17} Finally, many trials excluded patients below a minimum forced vital capacity (FVC) or a limiting score on a functional rating scale.^{2,3,5,7,8,16,17} These restrictive criteria might make clinical trial sample data inapplicable to the general ALS population. A prior study using an ALS clinical database to identify predictors of survival was limited by missing data points, excluding 92 of 247 patients from the analysis, and did not provide an estimate of the strength of the association between ALSFRS_r and mortality.¹⁸

Validating the ALSFRS_r as a predictor of survival time outside the clinical trial experience has two benefits. 1) It may encourage clinicians to accept that the results of trials using it as a primary outcome measure are applicable to the general ALS population. 2) In the clinical setting, it may provide an

From the Department of Neurology, College of Physicians and Surgeons (Drs. Kaufmann, Gordon, Rowland, and Mitsumoto, and M.L. DelBene and V. Battista), and the Department of Biostatistics, Mailman School of Public Health (Drs. Levy, Thompson, and Levin), Columbia University, New York, NY. Supported by an Irving Scholar Award (P.K.), K12 Award (P.K.), Muscular Dystrophy Association "Wings over Wall Street" (H.M.), NINDS R01 NS 48125 (P.K.), NINDS R01 NS48558 (G.L., J.L.P.T., B.L.).

Received February 10, 2004. Accepted in final form September 15, 2004.

Address correspondence and reprint requests to Dr. Petra Kaufmann, The Neurologic Institute, Columbia University, 710 W 168th Street, New York, NY 10032; e-mail: pk88@columbia.edu

38 Copyright © 2005 by AAN Enterprises, Inc.

Downloaded from www.neurology.org at Mitsubishi Pharma Corporation on August 5, 2011

easily administered instrument for better prognostication and management of ALS patients.

To study the validity of the total baseline ALSFRS_r score and subscores as a predictor of survival time beyond the constraints of a clinical trial, we analyzed longitudinal data from an ALS clinic population.

Methods. Patients and procedures. In December 1999, we began administering the ALSFRS_r to all patients who were cared for at the Eleanor and Lou Gehrig MDA/ALS Research Center in New York City, a tertiary care center. We prospectively collected data and included consecutive patients who came to the center for an initial visit between December 1999 and July 2003 with the diagnosis of suspected, possible, probable, or definite ALS according to the initial El Escorial Criteria.¹⁹ The number of patients cared for at the center has increased in recent years so that more patients were seen during the second half of the study period. Patients who came to the center during their diagnostic workup but subsequently received their ongoing care elsewhere were excluded. The protocol for this study was approved by the Columbia University Medical Center Institutional Review Board.

Between 1 and 6 months following their initial diagnostic consultation, patients were referred by one of the ALS center's physicians to receive their ongoing ALS care at the multidisciplinary ALS clinic. At the baseline visit to this clinic, we documented demographic and clinical information, including age, sex, and date and site of symptom onset. Symptom duration was defined as the time period between reported onset and baseline evaluation. Site of symptom onset was categorized into four groups (upper extremity, lower extremity, bulbar, or respiratory onset) according to the patient's report. In addition to the medical history and neurologic examination, the baseline evaluation included the ALSFRS_r and FVC. The original ALSFRS is a questionnaire-based, 10-item functional scale administered by an evaluator to the patient or, if the patient cannot communicate effectively, to an informant (spouse or other caregiver).¹⁹ The revised scale (ALSFRS_r) incorporates three items assessing respiratory function, replacing one item in the original ALSFRS. The ALSFRS_r contains 12 items rated from 0 (complete dependence for that function) to 4 (normal function), resulting in a total ALSFRS_r score ranging from 0 to 48. The items fall into four clinical domain subscores, each containing three items: 1) bulbar function, 2) fine motor function, 3) gross motor function, and 4) respiratory function.¹⁴

During the follow-up period, we collected information on date of death and tracheostomy for institution of permanent mechanical ventilation. Although we intended to see patients every 3 months, intervals between visits varied. In the terminal stages of the disease, many patients could not come to the center, but care was delivered remotely through telephone contact, e-mail, home visits, and in collaboration with home health care and hospice agencies.

All patients with 1) ALSFRS_r score at baseline visit and 2) known survival status were included in the analysis. Of 274 consecutive patients who had ALSFRS_r at baseline, 7 (2.6%) were excluded because we had no survival status information, leaving 267 patients for analysis. No significant differences were observed between excluded ($n = 7$) and included patients ($n = 267$) for age, sex, symptom duration, site of symptom onset, total ALSFRS_r score, or FVC. Seventeen of 267 patients (6.4%) were lacking information for FVC because spirometry was not performed if there were technical problems in patients with poor lip seal or impaired cognition or if there were time constraints in the busy multidisciplinary care setting.

Data analysis. We compared baseline demographic and clinical characteristics of ALS patients who died or had tracheostomy during follow-up and those who did not, using Student's t -test for continuous variables and a χ^2 test for categorical variables. When the assumption of normal distribution for a given baseline variable was not reasonable based on visual inspection of the histograms, we used the Wilcoxon's rank sum test instead of the t -test. Time to endpoint was the time from baseline to death or tracheostomy; patients who remained alive without tracheostomy were censored at study end (July 24, 2003). The association of the total ALSFRS_r score and subscores at baseline with death or tracheostomy was analyzed using Cox proportional hazards models, adjusting for age at baseline, sex, and symptom duration.²⁰ We also

investigated this association by including the total ALSFRS_r score together with potential confounding clinical variables, such as FVC (% predicted), riluzole use (ever vs never), and site of symptom onset, in separate Cox models. Finally, we included the total ALSFRS_r score and the other significant or clinically meaningful covariates in the same Cox model. Categorical variables were inserted into the Cox models as dummy variables. The Kaplan-Meier method was used to plot survival curves.²¹

Two sets of supplementary analyses were conducted. First, we fit two Cox models using 1) the ALSFRS_r score at each visit and 2) the ALSFRS_r score change from baseline at each visit (total ALSFRS_r score at baseline – total ALSFRS_r score at each visit) as time-dependent covariates in separate models. Because the interval and frequency of follow-up visits varied and many patients with advanced disease could not come to the center, we had to impute the ALSFRS_r score for 2,586 of 3,204 (81%) "monthly visits," as required by our choice of monthly intervals for the time-dependent covariate analysis. The imputation procedure used linear interpolation between two known ALSFRS_r scores. (For patients with only the baseline visit, a slope was calculated by using symptom duration and the ALSFRS_r score at baseline, and assuming a maximum score of 48 at symptom onset.)

Second, given the heterogeneity of the clinical manifestations of ALS, i.e., differences in the site of symptom onset and different patterns of spread to other body regions, we postulated that defining a most affected domain subscore of the ALSFRS_r for each patient might provide a sensitive alternative outcome measure for ALS trials. As a first step in assessing the most affected domain subscore as a possible outcome measure, we investigated the association of the most affected subscore of the ALSFRS_r with death or tracheostomy. The most affected ALSFRS_r subscore was defined as the lowest value at baseline evaluation among the fine motor, gross motor, bulbar, and respiratory clinical domain subscores for each patient. The most affected subscore was the gross motor subscore for 103 (38.6%) patients, fine motor for 70 (26.2%), bulbar for 50 (18.7%), and respiratory for 6 (2.2%). In 38 (14.2%) patients two domain subscores had equally low values.

All statistical analyses were predetermined with the exception of the Cox models with time-dependent covariates and an analysis stratifying the sample into two subsets of patients with total ALSFRS_r score above and below the median and including the total ALSFRS_r score in the models as a continuous variable.

Results. Demographic and clinical characteristics of ALS patients. A total of 103 (38.6%) of 267 patients died ($n = 79$) or had tracheostomy ($n = 24$). The mean duration of follow-up for the whole sample ($n = 267$) was 1.0 year (SD 0.7, median 0.9, minimum 0.01, maximum 2.6). The mean time to death or tracheostomy ($n = 103$) was 0.8 years (SD 0.6, median 0.7, minimum 0.01, maximum 2.3). Compared to the patients who were still alive without tracheostomy, those who died or went on permanent ventilation had significantly shorter symptom duration, lower baseline total ALSFRS_r score, and FVC. Patients who died or had tracheostomy also had respiratory onset significantly more often and upper extremity onset significantly less often than patients who did not (table 1).

Patients who died or had tracheostomy used noninvasive positive pressure ventilation (57.3% vs 22.0%, $p < 0.001$) or percutaneous endoscopic gastrostomy (PEG) (42.7% vs 11.0%, $p < 0.001$) more often than patients who remained alive without permanent ventilation. Ninety of 267 patients (33.7%) used riluzole during follow-up with no significant difference between the two groups (31.1% of those who died or had tracheostomy vs 35.4% of those who did not, $p = 0.5$).

Association of the baseline ALSFRS_r with mortality. Patients with a baseline total ALSFRS_r score below the median score of 38 had a 4.4-fold increased risk of death or tracheostomy compared to patients with a score above the median (HR: 4.38, 95% CI: 2.79 to 6.86, $p < 0.001$), adjust-

Table 1 Baseline demographic and clinical characteristics of ALS patients who died or had tracheostomy during follow-up compared to those who remained alive without tracheostomy

Variable	Deceased or tracheostomy, n = 103	Alive without tracheostomy, n = 164	Total, n = 267
Age, y	63.3 (13.5)	60.7 (12.5)	61.7 (12.9)
% Male	50.5	57.3	54.7
Age at onset, y	59.9 (13.6)	57.1 (13.1)	58.2 (13.3)
Symptom duration, y*	1.8 (1.6)	2.5 (3.4)	2.2 (2.9)
Site of symptom onset*			
Upper extremity†	20.4	39.0	31.8
Lower extremity	38.8	39.0	39.0
Bulbar	33.0	21.3	26.8
Respiratory†	7.8	0.6	3.4
Forced vital capacity (% predicted)*‡	60.1 (24.7)	79.8 (21.8)	72.1 (24.9)
ALSFRS _r scores			
Total (range 0–48)*	31.7 (7.7)	38.7 (7.1)	36.0 (8.1)
Fine motor subscore (range 0–12)*	7.0 (3.6)	8.9 (2.9)	8.1 (3.3)
Gross motor subscore (range 0–12)*	6.1 (3.4)	8.1 (3.2)	7.3 (3.4)
Bulbar subscore (range 0–12)*	8.6 (3.4)	10.3 (2.6)	9.6 (3.0)
Respiratory subscore (range 0–12)*	10.1 (2.4)	11.5 (1.2)	10.9 (1.9)
Most affected subscore (range 0–12)*	4.4 (2.6)	6.8 (2.8)	5.9 (3.0)

Values are mean (SD) or %.

* $p < 0.05$ for the comparison of deceased or tracheostomy vs alive without tracheostomy.

† $p < 0.05$ for the comparison of individual sites of symptom onset adjusting for multiple comparisons.³⁰

‡ Total n = 250.

ALSFRS_r = Amyotrophic Lateral Sclerosis Functional Rating Scale-revised.

ing for age at baseline, sex, and symptom duration. The mean survival time for patients with baseline total ALSFRS_r above the median was 25.2 months (SE 1.0), compared to 14.6 months (SE 1.0, median survival 14.2) for those with baseline total ALSFRS_r score below the median. When patients were categorized according to quartiles of the total baseline ALSFRS_r score, the risk of death or tracheostomy increased progressively from the highest to the lowest quartile (test for linear trend, $p < 0.001$) (table 2 and figure, A).

Both the total ALSFRS_r score (HR: 0.91, 95% CI: 0.89 to 0.93, $p < 0.001$) and the FVC (HR: 0.97, 95% CI: 0.97 to 0.98, $p < 0.001$) were predictors of death or tracheostomy when included as continuous variables in separate Cox models. When both the total ALSFRS_r score and the FVC were included in the same model, both remained significant predictors of death/tracheostomy. Similarly, the association of the total ALSFRS_r score with death or

tracheostomy was not changed by including riluzole use or site of symptom onset in the Cox models (see table 2).

We also investigated the association of the total ALSFRS_r score at baseline (as a continuous variable) with death or tracheostomy separately for the subsets of patients with total ALSFRS_r score above and below the median (≥ 38 and < 38). The total baseline ALSFRS_r score remained a predictor in both subsets of patients (HR: 0.71, 95% CI: 0.59 to 0.84, $p < 0.001$ for patients with ALSFRS_r score above the median and HR: 0.95, 95% CI: 0.92 to 0.98, $p = 0.002$ for patients with ALSFRS_r score below the median).

When we analyzed the four subscores of the ALSFRS_r instead of the total ALSFRS_r score, the respiratory and gross motor subscores were independent significant predictors of death/tracheostomy (see table 2). The respiratory subscore showed a correlation with the FVC (Pearson correlation, $r = 0.53$, $p < 0.001$).

In a final model including all relevant demographic and clinical covariates, age at baseline, symptom duration, total ALSFRS_r score, and site of symptom onset were independent significant predictors of mortality in this ALS clinic population. For each one-point decrease in the total baseline ALSFRS_r score, there was a 7% increase in the risk of death or tracheostomy (HR: 0.93, 95% CI: 0.90 to 0.96, $p < 0.001$) (table 3).

Supplementary analyses. We fit two Cox models with time-dependent covariates, adjusting for age at baseline, sex, and symptom duration at baseline. In the first model, the total ALSFRS_r score at each study visit was a predictor of death/tracheostomy (HR: 0.90, 95% CI: 0.89 to 0.92, $p < 0.001$). In the second model, we included the total ALSFRS_r score at baseline as a time-fixed covariate and the ALSFRS_r score change from baseline at each visit as a time-dependent covariate. In this latter model, the total ALSFRS_r score at baseline (HR: 0.91, 95% CI: 0.89 to 0.94, $p < 0.001$) and the ALSFRS_r score change at each visit (HR: 1.12, 95% CI: 1.09 to 1.15, $p < 0.001$) were independent predictors of death/tracheostomy.

When we investigated the association of the most affected ALSFRS_r subscore with death/tracheostomy, we observed a 4.4-fold increased risk for patients with the most affected subscore below the median compared to those with the most affected subscore above the median. The risk increased progressively from the highest to the lowest quartile (test for linear trend, $p < 0.001$). In a Cox model adjusting for age at baseline, sex, and symptom duration, there was a 24% increase in the risk of death/tracheostomy for each one-point decrease in the most affected subscore (HR: 0.76, 95% CI: 0.70 to 0.81, $p < 0.001$) (see table 2 and figure, B).

Finally, we used a backward stepwise selection procedure (entry criterion: $p < 0.05$, exclusion criterion: $p > 0.1$) to select the best predictors among the four subscores of the ALSFRS_r (fine motor, gross motor, bulbar, and respiratory) and the most affected subscore. In this analysis, the respiratory (HR: 0.80, 95% CI: 0.73 to 0.87, $p < 0.001$) and most affected (HR: 0.79, 95% CI: 0.73 to 0.85, $p < 0.001$) subscores were retained in the model.

Discussion. Based on our data, the total ALSFRS_r score at initial visit strongly predicted survival time in an ALS clinic population, after adjustment for age at baseline, sex, and symptom duration. We also

Table 2 Association of the baseline ALSFRS_r and other clinical characteristics with death or tracheostomy, from Cox proportional hazards models adjusting for age at baseline, sex, and symptom duration (n = 267)

Model	Variable	Hazard ratio (95% CI)	p Value
1	Total ALSFRS _r score (dichotomized at the median)		
	≥38	1.00 (Reference)	
	<38	4.38 (2.79–6.86)	<0.001
2	Total ALSFRS _r score quartiles		
	≥43	1.00 (Reference)	
	≥38 and <43	7.08 (2.12–23.66)	0.001
	≥33 and <38	12.51 (3.81–41.08)	<0.001
	<33	27.78 (8.57–90.07)	<0.001
3	Total ALSFRS _r score	0.91 (0.89–0.93)	<0.001
4*	Total ALSFRS _r score	0.94 (0.91–0.98)	<0.001
	Forced vital capacity (% predicted)	0.99 (0.98–1.00)	0.02
5	Total ALSFRS _r score	0.91 (0.89–0.93)	<0.001
	Riluzole use (ever vs never)	0.92 (0.60–1.41)	0.7
6	Total ALSFRS _r score	0.91 (0.89–0.93)	<0.001
	Site of symptom onset		
	Upper extremity	1.00 (Reference)	
	Lower extremity	1.28 (0.73–2.23)	0.4
	Bulbar	1.91 (1.06–3.46)	0.03
	Respiratory	8.44 (3.68–19.35)	<0.001
7	Fine motor ALSFRS _r subscore	0.95 (0.88–1.03)	0.2
	Gross motor ALSFRS _r subscore	0.91 (0.84–0.99)	0.02
	Bulbar ALSFRS _r subscore	0.94 (0.88–1.01)	0.08
	Respiratory ALSFRS _r subscore	0.79 (0.72–0.87)	<0.001
8	Most affected ALSFRS _r subscore (dichotomized at the median)		
	≥7	1.00 (Reference)	
	<7	4.44 (2.73–7.22)	<0.001
9	Most affected ALSFRS _r subscore quartiles		
	≥9	1.00 (Reference)	
	≥7 and <9	4.48 (1.32–15.22)	0.02
	≥4 and <7	10.33 (3.18–33.87)	<0.001
	<4	20.60 (6.31–67.30)	<0.001
10	Most affected ALSFRS _r subscore	0.76 (0.70–0.81)	<0.001

* n = 250.

ALSFRS_r = Amyotrophic Lateral Sclerosis Functional Rating Scale–revised.

found an independent effect of the baseline total ALSFRS_r score on death/tracheostomy in Cox models including FVC and riluzole use. These findings are consistent with the ALS clinical trial results.^{2,7,8,14,16,17} The robust association between ALSFRS_r and death/tracheostomy was remarkable given that the clinic setting is less controlled than the clinical trial environment and does not provide consistent raters or continuous training and evaluation of raters. Also,

our experience indicates that the ALSFRS_r can be successfully administered in a busy multidisciplinary clinic. Larger studies are needed to obtain narrower CIs for relative risk estimates and thus allow better assessment of the sensitivity of the ALSFRS_r to predict small changes in mortality.

Among the ALSFRS_r subscores, the respiratory score was the strongest predictor of survival time, as expected because death in ALS is ultimately due to

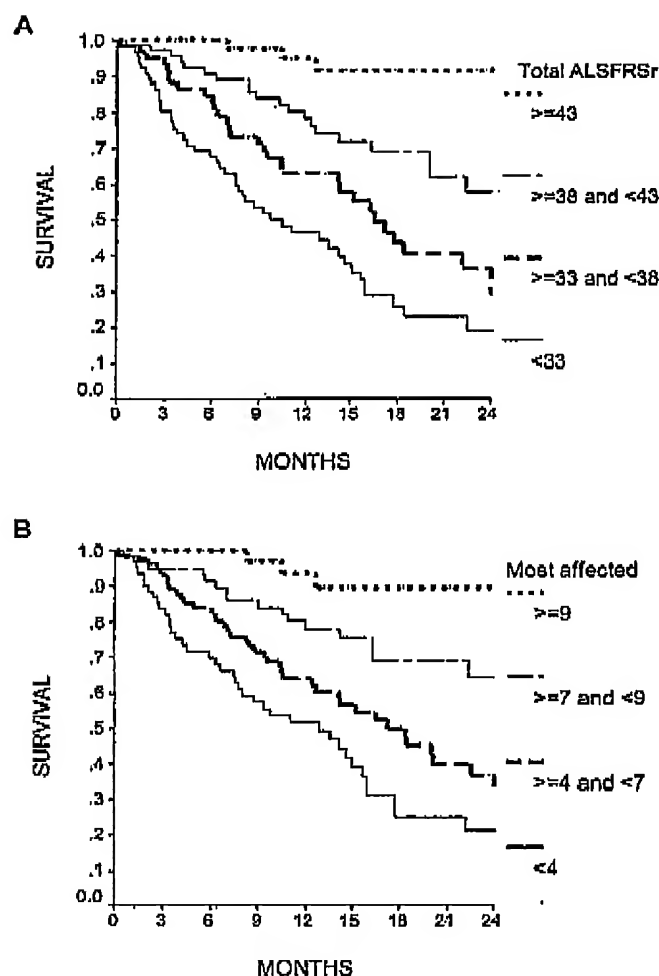


Figure. Kaplan-Meier survival plots (endpoint: death or tracheostomy) in an amyotrophic lateral sclerosis clinic population ($n = 267$), according to quartiles of the total Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS_r) score (A) and the most affected subscore of the ALSFRS_r (B).

respiratory failure. While respiratory subscore and FVC were correlated, the respiratory subscore did not account for much of the FVC variation ($r = 0.53$, $r^2 = 0.28$). The correlation in our study was higher than in the BDNF clinical trial ($r = 0.33$),¹⁴ which may in part be attributed to the wider range of disease severity in our patients. The FVC was a significant predictor of mortality in several clinical trials,^{16,17} but not in this study when other clinically meaningful covariates were included in the model. Symptom duration at baseline visit was a significant predictor of survival time (shorter duration was associated with higher mortality) in our study, as in others.^{22,24} A possible interpretation is that symptom duration at first visit may be a measure of the rate of disease progression, because patients who have more rapidly progressive symptoms go to physicians sooner.

Table 3 Predictors of death or tracheostomy in an ALS clinic population ($n = 250$)*

Variable	Hazard ratio (95% CI)	p Value
Age at baseline, y	1.02 (1.01–1.04)	0.01
Male vs female	0.85 (0.53–1.35)	0.5
Symptom duration, y	0.74 (0.63–0.87)	<0.001
Total ALSFRS _r score	0.93 (0.90–0.96)	<0.001
Forced vital capacity, % predicted	0.99 (0.98–1.01)	0.3
Riluzole use, ever vs never	0.85 (0.54–1.33)	0.5
Site of symptom onset		
Upper extremity	1.00 (Reference)	
Lower extremity	1.17 (0.66–2.07)	0.6
Bulbar	1.81 (0.99–3.33)	0.05
Respiratory	6.52 (2.72–15.60)	<0.001

* All variables were included in the same Cox proportional hazards model.

ALSFRS_r = Amyotrophic Lateral Sclerosis Functional Rating Scale-revised.

The strong association of the most affected subscore of the ALSFRS_r with mortality suggests that a measure that considers the clinical heterogeneity of ALS provides an alternative outcome measure, which may prove to be more sensitive than the total ALSFRS_r score for ALS clinical trials.

The main strength of our study is that, compared to patients in clinical trials who must meet restrictive inclusion criteria, our patient sample is probably more representative of the general ALS population. Our patients, who attend a tertiary ALS center, may be self-selected by access to information and medical care, although some of them attended a clinic for the poor. Also, our study population is not an incidence cohort and thus further research on incidence cases is needed to determine the validity of the ALSFRS_r as a predictor of mortality in the general ALS population.

Our study has limitations. Our sample presented a relatively long mean symptom duration (2.2, SD 2.9 years) and low mean ALSFRS_r score (36.0, SD 8.1) at baseline, which might indicate that our findings are not applicable to a less severe clinic sample of ALS patients. However, the effect of the ALSFRS_r was even stronger when we analyzed separately the subsample of patients with ALSFRS_r score above the median. Noninvasive, positive pressure ventilation²⁵ and PEG²⁶ are associated with increased mortality in ALS trials and a clinical database,²⁷ implying that these therapies are markers of advanced disease. A population-based study²⁸ has confirmed the increased survival in patients taking riluzole, reported in clinical trials.¹⁴ However, our data did not allow detailed analyses of these therapeutic interventions, because accurate data on timing or compliance with these interventions were not recorded in sufficient detail. It has also been suggested that the decline in

ALSFRS scores for a group of patients is a stronger predictor of mortality than the initial score.^{16,17} Although our primary analysis used the initial ALSFRS score, we have conducted secondary analyses with ALSFRS as a time-dependent covariate and found that the ALSFRS at each visit as well as the change in ALSFRS score from baseline (independently of the baseline ALSFRS score) are significant predictors of survival time in ALS. These analyses suggest that changes over time in the ALSFRS score reflect disease progression, and thus further support its role as a predictor of survival time in ALS. However, the results of these secondary time-dependent analyses have limitations since data for most of the visits had to be imputed, because the interval and frequency of follow-up visits varied in our sample. Many patients with advanced disease could not come to the center, and telephone administration of the ALSFRS has not been part of our clinical practice.

Whereas further research is needed to determine whether the ALSFRS has sufficient sensitivity to detect small changes in mortality, the potential advantages of the ALSFRS for clinical trials are shorter follow-up period (compared to mortality as outcome measure) and wider participation of patients and clinicians outside University-based ALS centers (compared to outcome measures requiring special equipment such as quantitative muscle strength testing). These are important considerations for ALS clinical trials given the limited pool of patients and the number of new treatments awaiting testing.²⁰

References

1. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet* 1996;347:1425-1431.
2. A controlled trial of recombinant methionyl human BDNF in ALS: The BDNF Study Group (Phase III). *Neurology* 1999;52:1427-1433.
3. Groeneveld CJ, Veldink JH, van der Tweel I, et al. A randomized sequential trial of creatine in amyotrophic lateral sclerosis. *Ann Neurol* 2003;53:437-445.
4. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med* 1994;330:585-591.
5. A double-blind placebo-controlled clinical trial of subcutaneous recombinant human ciliary neurotrophic factor (rHCNTF) in amyotrophic lateral sclerosis. ALS CNTF Treatment Study Group. *Neurology* 1996;46:1244-1249.
6. Miller RG, Moore D, Young LA, et al. Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis. WALS Study Group. Western Amyotrophic Lateral Sclerosis Study Group. *Neurology* 1996;47:1383-1388.
7. Miller RG, Moore DH, 2nd, Gelinas DF, et al. Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 2001;56:843-848.
8. Cudkowicz ME, Shefner JM, Schoenfeld DA, et al. A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis. *Neurology* 2003;61:466-464.
9. Lai EC, Felice KJ, Festoff BW, et al. Effect of recombinant human insulin-like growth factor-I on progression of ALS. A placebo-controlled study. The North America ALS/IGF-I Study Group. *Neurology* 1997;49:1621-1630.
10. Borasio GD, Robberecht W, Leigh PN, et al. A placebo-controlled trial of insulin-like growth factor-I in amyotrophic lateral sclerosis. European ALS/IGF-I Study Group. *Neurology* 1998;51:583-586.
11. Shefner JM, Cudkowicz ME, Schoenfeld D, et al. and the NEALS Consortium. Clinical trial of creatine in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003;4(suppl):28, C31.
12. Brooks BR. Functional scales: summary. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2002;3(suppl 1):S13-18.
13. The Amyotrophic Lateral Sclerosis Functional Rating Scale. Assessment of activities of daily living in patients with amyotrophic lateral sclerosis. The ALS CNTF treatment study (ACTS) phase I-II Study Group. *Arch Neurol* 1996;53:141-147.
14. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J Neurol Sci* 1999;169:13-21.
15. Cedarbaum JM, Stambler N. Performance of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) in multicenter clinical trials. *J Neurol Sci* 1997;152 suppl 1:S1-9.
16. Moore DH, Miller RG, WALS Study Group, ALS CARE Study Group. ALSFRS as a measure of disease progression and survival. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003;4(suppl 1):42, C60.
17. Traynor BJ, Zhang H, Shefner JM, Schoenfeld D, Cudkowicz CE. Functional outcome measures as a clinical trial endpoint in ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003;4(suppl 1):42, C61.
18. Magnus T, Bock M, Giesse R, Puls I, Naumann M, Toyka KV. Disease progression in amyotrophic lateral sclerosis: predictors of survival. *Muscle Nerve* 2002;25:709-714.
19. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. *J Neurol Sci* 1994;124 suppl:66-107.
20. Cox DR. Regression models and life tables. *J R Statist Soc B* 1972;34:187-220.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
22. Turner M, Al-Chalabi A. Early symptom progression rate is related to ALS outcome: a prospective population-based study. *Neurology* 2002;59:2012-2013; author reply 2013.
23. Chio A, Mora G, Leone M, et al. Early symptom progression rate is related to ALS outcome: a prospective population-based study. *Neurology* 2002;59:99-103.
24. Turner MR, Bakker M, Sham P, Shaw CE, Leigh PN, Al-Chalabi A. Prognostic modelling of therapeutic interventions in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2002;3:15-21.
25. Cedarbaum JM, Stambler N. Disease status and use of ventilatory support by ALS patients. BDNF Study Group. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2001;2:19-22.
26. Kasaralis EJ, Sciarata D, Hill R, Fuller C, Stambler N, Cedarbaum JM. A retrospective study of percutaneous endoscopic gastrostomy in ALS patients during the BDNF and CNTF trials. *J Neurol Sci* 1999;160:118-125.
27. Mitsumoto H, Davidson M, Moore D, et al. Percutaneous endoscopic gastrostomy (PEG) in patients with ALS and bulbar dysfunction. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003;4:177-185.
28. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. An outcome study of riluzole in amyotrophic lateral sclerosis—a population-based study in Ireland, 1996-2000. *J Neurol* 2003;260:473-479.
29. Bruijn LI, Trotti D, Kristal BS, et al. Pre-clinical trials of three FDA-approved compounds in a mouse model of ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003;4(suppl 1):76, C96.
30. Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions. Hoboken, NJ: Wiley Interscience, 2003.